REMARKS

Upon entry of this amendment, claims 1-10, 12-35, 49, 51-62 and new claims 63-89 are pending. The specification has been amended to correct an obvious typographical error. Claims 1, 2 and 49 are amended to more clearly recite the invention and to remove redundant phraseology. Support for the amendments can be found throughout the specification, in particular at page 11, line 22 through page 12, line 17 (sterilization), page 18, lines 9 through page 23, line 12 (particle size), and page 25, lines 10-14 (concentration). Support for the new claims can be found at the same places and additionally at page 18, line 3 (sterile filtration). Applicants assert that no new matter has been introduced as a result of these amendments. Applicants wish to thank the Examiner for the courteous interview conducted on June 25, 2003, a summary of which is already of record.

Rejections Under 35 U.S.C. §103

Claims 1-10, 12-35, 49 and 51-62 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthamol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147) or Sankaram *et al.* (5, 766, 627) in view of Lenke *et al.* (5,948,441). The Examiner has stated that all of the primary references teach processes of making multivesicular liposomes, but that they do not teach cross-flow filtration and making a sterile preparation.

The Examiner further has characterized the secondary reference, Lenke *et al.*, as teaching cross-flow filtration used for selection of large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population. The Examiner also has stated that Lenke *et al.* teaches various modes of administration and sterilization. The Examiner then reasons that the use of cross-flow filtration would have been an obvious step in addition to the processes of the primary references because Lenke *et al.* teaches its use in the preparation of liposomes, and because one of ordinary skill in the art would realize that such preparations should be sterilized.

The Examiner has stated that most of Applicants' arguments previously have been addressed. Applicants disagree. The Examiner additionally has indicated that sterilization of

compositions intended for human administration is well known in the art. Applicants have never denied this. Applicants have addressed the issue of sterilization to distinguish that cross-flow filtration is not used for this purpose according to the present claims, as was previously alleged by the Examiner. Moreover, the Examiner has indicated that it is well known that there is a relationship between energy input and particle size. Again, Applicants have addressed the issue of particle size to distinguish that cross-flow filtration is not used for particle size selection according to the present claims.

The primary references disclose methods of producing multivesicular liposomes (MVLs). As previously indicated, these methods disclose centrifugation as a means of adjusting the final concentration of the composition and removing the unwanted buffer and unencapsulated drug. The present invention discloses a novel method whereby cross-flow filtration is used to achieve these objectives, thereby resulting in a higher yield and decreased process time.

The secondary reference, Lenke *et al.*, describes the use of cross-flow filtration for use in size separation of pre-formed particles (See '441 at 1:14-16). In this process, certain relatively small particles are separated from larger particles as they pass through appropriately sized filter pores. Particles too large to pass through the pores are retained. The liposome preparation methods disclosed by Lenke *et al.* result in the formation of liposomes having an undesirably wide distribution of particle sizes (See '441 at 4:12-13). Lenke *et al.* teaches that "there remains a difficulty in the art of obtaining a homogeneous population of liposomes..." (See '441 at 4:65-67). In stark contrast, no size separation step is required in the claimed processes. The present claims recite processes whereby the size of the multivesicular liposomes is *pre-determined* and has *uniform size distribution*. The pre-determined liposome sizes are produced according to process parameters *at the time of liposome formation*. Thus, no post-formation size sorting is required, and the resulting composition can be immediately administered to patients.

Although Lenke *et al.* describes a number of liposome species including unilamellar, multilamellar (MLV), sonicated unilamellar (SUV), plurilamellar (SPLV), frozen and thawed multilamellar (FATMLV) and reverse-phase evaporation vesicles (REV), Lenke *et al.* does not disclose multivesicular liposomes even though they were known in the art at the time of that

invention. There is good reason for this omission of MVLs from the laundry list of liposomes referenced in the Lenke *et al.* disclosure.

It is well known in the art that multivesicular liposomes are unique particles possessing characteristics that distinguish them from other types of liposomes. These characteristics include relatively massive size, non-concentric vesicle arrangement, and exceptional encapsulation and release properties. These characteristics are the direct result of the distinctive processes used for preparing multivesicular liposomes. By omission of the multivesicular liposome species, Lenke *et al.* fails to disclose the use of cross-flow filtration for the preparation of multivesicular liposomes. Additionally, as discussed more fully below, cross-flow filtration is not useful for size separation of multivesicular liposomes, nor is it employed for that effect in the instant invention.

The present claims recite sterilization of the liposomes either at the time of formation through use of sterile starting materials, or after cross-flow filtration, prior to filling. None of the references, either alone or in any combination, teach the ability to control and pre-determine multivesicular liposome size at the liposome formation step of the production process, thereby eliminating the need for post-formation size sorting. Additionally, none of the references teach the ability to adjust final concentration of the composition or remove unwanted buffer and unencapsulated drug by use of cross-flow filtration. Lenke *et al.* does not supply these missing elements and in fact teaches away from the control of liposome size at the formation stage, since Lenke *et al.* is directed to methods for post-formation size selection.

Applicants point out that even if cross-flow filtration were desirable for size selection according to the present invention (which it is not), 10 μm is the upper limit of the particle sizes for which the Lenke *et al.* cross-flow filtration technique is useful (column 8, lines 53-55). In contrast, multivesicular liposomes are generally larger than 10 μm and therefore cross-flow filtration would not be useful as a means for controlling particle size for these very large liposomes. Cross-flow filtration is used for the presently claimed process for the opposite result, *i.e.,* Applicants' desire to completely retain the MLV particles in a container while moving fluids in and out. Accordingly, there would have been absolutely no motivation to combine the

primary and secondary references, and such combination fails to teach or suggest the present invention.

The Examiner has stated that the motivation for using cross-flow filtration as taught in Lenke *et al.* need not be the same as in the present invention. Applicants assert, however, that there must be some identifiable motivation. Here, there is motivation not to combine the Lenke *et al.* reference with the primary references. The method disclosed by Lenke *et al.* would clearly be inappropriate for MVLs, which are extremely large liposomes. The disclosure of Lenke *et al.*, specifically teaches away from using cross-flow filtration, as there is no desire for size selection at any stage in the present invention. The claimed process produces particle sizes that are predetermined and the resulting composition comprises particles of uniform size distribution, requiring no size selection step. Moreover, Lenke *et al.* does not teach or suggest use of cross-flow filtration for the claimed purposes. Therefore, Applicants' claims are patentable over the cited references. There is no motivation to combine the primary and secondary references, and even if combined, the references do not teach or suggest the present invention. Accordingly, Applicants respectfully request reconsideration and removal of this rejection.

Claims 1-10, 12-35, 49 and 51-53 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthamol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147) or Sankaram *et al.* (5, 766, 627) in view of Lenke *et al.* (5,948,441) in further view of Kwasiborski *et al.* (6,033,708), Fenske *et al.* (5,837,282), Mehl, Sr. *et al.* (5,885,260), Castor *et al.* (5,776,486), and Moynihan (5,589,189) by themselves or in combination. The Examiner has stated that each of the tertiary references teach methods of sterilization and that one of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the tertiary references each teach methods that involve the production of sterile liposomes. Applicants respectfully disagree for the following reasons.

As previously discussed, there is no motivation to combine the primary and secondary references. Even if such motivation existed, the combination of the primary and secondary references does not teach or suggest the present invention. In particular, none of the references discloses the control of particle size at the tim of liposome formation, with subsequent cross-

flow filtration unrelated to size selection. For reasons already of record, none of the tertiary references teaches or suggests these limitations missing from the primary and secondary references. Moreover, just as the cross-flow filtration step of the instant invention does not relate to particle size selection, it is not required or even capable of use for sterilization of the resulting composition due to the pore sizes of the preferred filters. Accordingly, Applicants respectfully request reconsideration and removal of this rejection.

Applicants maintain that all pending claims are allowable and respectfully request such indication.

Please apply any charges or credits to Deposit Account No.50-2613.

Respectfully submitted,

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